REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and following remarks.

Status of the claims

Claims 1-47 were canceled.

New claims 48-59 were added by the amendment of April 30, 2004.

Claims 56, 58, and 59 are herein canceled.

Claim 48 is herein amended to add the language "wherein said compound has a K_i or IC_{50} of less than 100 μM, as determined in an assay that measures inhibition of binding between alpha-9 integrin and alpha-9 integrin ligand." The amendment clarifies the claimed invention. Support for the amendment can be found, for example, at page 5, lines 9-12; page 8, lines 20-26; and throughout pages 19-22 and 29-30, of the specification.

Claim 51 has been rewritten in independent form by incorporating the language of claims 48 and 49.

Claim 55 is herein amended to delete the recitation of pharmaceutically effective dosage, as suggested by the Examiner in the Office Action of July 2, 2004 at page 13 page 14.

Following amendments, claims 48-55 and 57 will be pending in the application.

Provisional obviousness-type double-patenting rejection

Applicants request that the obviousness-type double-patenting rejection be held in abeyance until allowable subject matter is indicated.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

Claims 48-59 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the claimed method, which comprises the step of binding an α_9 integrin antagonist to the α_9 integrin receptor. Specifically, the Patent Office asserted that **(A)** the structure/function relationship of VLA-4 antagonism is unpredictable and **(B)** treatment of inflammatory conditions is unpredicatable. Office Action of July 28, 2004 at page 3+.

These rejections are traversed because the level of predictability in the art is far higher than the Office Actions asserts, particularly with respect to ligand binding among the α_4 and α_9 integrins. Therefore, one skilled in the art would be able to practice the claimed methods, given the instant disclosure.

(A) The Patent Office has provided a number of references that report unpredictability in structure/function and binding characteristics of various ligands and receptors. Of these references, Dutta *et al*, Arrhenius *et al.*, Komoriya *et al.*, Haworth *et al.*, and Yang *et al.* appear to relate to the α_4 integrins, while Haubner *et al.* relates to the distinct αIIb and αV families (references of record). However, the level of unpredictability in the art is not as high as these references imply and undue experimentation is not required to practice the methods of the claimed invention.

First, as set forth in the previous Response of April 30, 2004 at page 10, the level of predictability in the art with respect to $\alpha_4\beta_1$-integrin (VLA-4) receptor-ligand interactions is not relevant to the pending claims. Applicants have already identified compounds that bind to VLA-4 (specification at, *e.g.*, page 5, lines 1-8; page 7, lines 7-12; page 9, lines 17-24; page 13, line 16 – page 15, line 8; page 17, line 14 – page 19, line 9 (including Table 1); page 22, lines 3-9; page 29, lines 22-26; and Example 1). Therefore, the compounds described in the specification are experimentally validated VLA-4 ligands. Whether the binding of certain compounds to VLA-4 is predictable or unpredictable is moot.

The relevant question is whether proven $\alpha_4\beta_1$ (VLA-4) ligands are likely to be ligands (or modulate the binding the binding of known ligands) for the α_9 integrins. According to the

specification, compounds that modulate the binding of $\alpha_4\beta_1$ integrins (such as VLA-4) to its ligands are generally good candidates for modulating the binding of α_9 integrin to its ligands. Specification at, *e.g.*, page 13, line 29 - page 14, line 5.

There is ample support for this assertion in the scientific literature because α_4 and α_9 integrins are known to share common ligands. It naturally follows that such shared ligands, if administered to a mammalian patient, would modulate the binding of α_9 integrins to endogenous ligands.

Based on their biological properties, the α_4 and α_9 integrins have been classified separately from all other integrins. Unlike most integrins, which bind ligands via the classical RGD motif, α_4 and α_9 integrins bind ligands via a cryptic motif, comprising the sequence SVVYGLR, which notably lacks the acidic residue of the RGD motif. Green *et al.* (2001) *FEBS Letters* 503:75-79; Takahashi *et al.* (2000) *J. Biol. Chem.* 275:23589-95. Thus, the α_4 and α_9 integrins are known to share ligand binding features that distinguish them from the other families of integrins.

Experimentally, α_4 and α_9 integrins have been shown to share a large repertoire of ligands. Such ligands include

- osteopontin,
- vascular cell-adhesion molecule-1 (VCAM-1),
- tissue-type transglutaminase (tTG),
- blood coagulation factor XIII,
- a cell adhesion molecule in the immunoglobulin superfamily (L1CAM)
- the pro-form of von Willebrand factor (pp-vWF), and
- the EIIIA segment of fibronectin.

Zhu *et al.* (2002) *Biology of Reproduction* 66:1193-1202; Takahashi *et al.* (2000) *J. Biol. Chem.* 275:23589-95; Green *et al.* (2001) *FEBS Letters* 503:75-79; Liao *et al.* (2002) *J. Biol. Chem.* 277:14467-74; provided as Exhibit A.

Thus, given a compound disclosed to bind to an α_4 integrin, such as VLA-4, one skilled in the art would have good reason to believe that the same compound would bind to α_9 integrin. By no means is the likelihood of α_4 and α_9 integrins sharing common ligands as remote as the

Office Action suggests. To the contrary, the α_4 and α_9 receptors appear to share a binding motif that is unique among the integrins, and to which a number of ligands are known to bind.

Moreover, in the interest of expediting prosecution, claim 48 has been amended to recite that "the claimed compound "has a K_i or IC_{50} of less than 100 μM, as determined in an assay that measures inhibition of binding between alpha-9 integrin and alpha-9 integrin ligand." This language, and the assays to which it refers, are fully supported by the specification, for example, at page 5, lines 9-12; page 8, lines 20-26; and throughout pages 19-22, 29-30. Performing these assays would not require undue experimentation and the scope of the resulting compounds would not be unduly broad in view of the requirements imposed by the additional claim language. For this reason alone, the outstanding rejection should be withdrawn.

In addition, claim 51 has been rewritten in independent form. Amended claim 51 is now drawn to compounds that have been explicitly identified in the specification. The outstanding enablement rejection will, presumably, not apply to amended claim 51, which should be allowable.

(B) The Office Action also provides a number of references purported to show unpredictability in the art with respect to treating inflammatory conditions. As discussed in the previous Response of April 30, 2004, Applicants are unable to appreciate the logic of imputing the failure of other to instant invention. There are sound scientific arguments in support of the success of the instant invention, which may have been overlooked by the Patent Office.

As would be expected of integrins associated inflammation, α_9 receptors are known to be expressed on the surface of neutrophils and keratinocytes but are absent on the surface of fibroblasts. Liao *et al.* (2002) *J. Biol. Chem.* 277:14467-74. α_9 receptors are believed to play a role in transendothelial leukocyte migration. Takahashi *et al.* (2000) *J. Biol. Chem.* 275:23589-95 and references within. Moreover, blocking ligand binding to $\alpha_9\beta_1$ integrin is known to reduce neutrophil chemotaxis. Green *et al.* (2001) *FEBS Letters* 503:75-79 and references within.

Therefore, given the available scientific information, there can be no doubt that a skilled artisan would reasonably ascertain that α_9 integrins are involved in inflammatory diseases and

that blocking the binding of ligands to α_9 receptors reduces leukocyte invasiveness. It is, therefore, a misinterpretation of the scientific evidence to assert that the level of predictability in the art makes impossible predictions relating to the biological effects of modulating ligand binding to α_9 integrin. This is clearly not the case.

Notwithstanding the allegations by the Patent Office to show unpredictability in the art, scientific evidence clearly shows that α_4 and α_9 integrins share common ligands and that α_9 integrins are associated with leukocyte invasion and inflammation. Therefore, one skilled in the art would be able to practice the methods of the claimed invention, without undue experimentation, because the essential information is disclosed in the specification. For at least these reasons, Applicants request withdrawal of the enablement rejection.

In the interest of expediting prosecution, the phrase "pharmaceutically effective dosage" has been deleted from claim 55, as suggested by the Examiner at page 13 – page 14 of the Office Action.

Rejections under 35 U.S.C. § 112, second paragraph

(A) Claims 56, 58, and 59 were rejected because they depended from canceled claims.

Claims 56, 58, and 59 have been canceled.

(B) Claims 48-53 were rejected as allegedly being indefinite with respect to the recited inflammatory conditions. The rejection is traversed.

The specification provides an abundance of support for inflammatory diseases, disorders, and conditions, at, *e.g.*, page 22, line 26 – page 26, line 19.

(C) Claim 55 was rejected as allegedly being indefinite with respect to the phrase "pharmaceutically effective."

The offending language has been deleted.

(D) Claim 59 was rejected as lacking antecedent basis for the phrase "alpha-4/beta-1."

Claim 59 has been canceled.

CONCLUSION

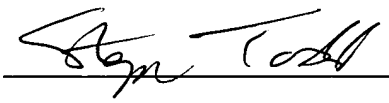
Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date: December 2, 2004

By 

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